REMARKS

Claims 46-58 are currently pending and Claims 55-58 have been withdrawn from consideration. Claims 46-54 have been rejected. Claims 46 and 48 and the specification have been amended without prejudice.

The Office Action acknowledged the claim for priority based upon applications P4403522.5, P4401629.8, and P4418091.8. It was noted, though, that certified copies of these applications had not been submitted. Applicant has attached translations of the priority documents. The original certified priority documents were filed in U.S. Serial No. 08/374,468, filed January 18, 1995.

The Office Action objected to the specification because it does not list the appropriate SEQ ID NOS in the description of Figures 1 and 2. Applicant has amended the description of said Figures accordingly, and respectfully requests that this rejection be withdrawn.

The Office Action also requested that a reference to the U.S. priority applications be inserted into the first sentence of specification of the application. Applicant has complied with this request and requests that this objection be withdrawn as well.

Claims 46-54 were rejected under 35 U.S.C. 112, first paragraph, as new matter. In particular, the Office Action stated that the claim language regarding "(1) a peptide/peptide derivative of at least 6, 8, or 10 amino acids from one of SEQ ID NO: 19-39 and having at most 25 amino acids and includes anchor positions for binding to DR3 or DR4" is new matter.

The language of these claims can be broken into at least the following elements: (1) a peptide or peptide derivative, (2) with a length of at least 6, 8, or 10 amino acids from one of SEQ ID NO: 19-39, (3) having at most 25 amino acids, and (4) including anchor positions for binding to DR3 or DR4.

Applicant observes that element (1) is disclosed in a number of the originally filed claims, such as Claim 1. Applicant also observes that the length requirements of element (2) were present in originally filed Claims 1, 3, and 4, respectively. The 25 amino acid length requirement of element (3) was contained in original Claim 5. Lastly, it appears that element (4) was claimed in original Claim 10. Additionally, Applicant notes that the sequences of SEQ ID NO: 19-39 relate to the sequences of original Figures 1 and 2. These sequences were contained in original Claim 1 as feature (c). Because the original claims and figures are part of the disclosure, these elements cannot be new matter because they were disclosed in the original filing. Thus, Applicant respectfully requests that this rejection be withdrawn.

Claims 46-54 were rejected under 35 U.S.C. 112, first paragraph, because the specification allegedly did not provide an adequate written description of the claimed invention. The Office Action contended that the specification does not convey that the Applicant had possession of the following at the time of invention: (1) a peptide consisting of between 6 and 25 amino acids comprising at least 6 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, and 19-39, including those wherein the peptide includes anchor positions for binding to alleles of MHC class II molecules DR3 and DR4, (2) a peptide or derivative thereof with a length between 6 and 25 amino acids which exhibits a specificity or/and affinity which is

essentially equivalent to that of the peptide in (1) above, and/or includes anchor positions for binding to alleles of MHC class II molecules DR3 or DR4 and/or as pertains to SEQ ID NO: 19-39, has a length of at least 8 or 10 amino acids, and (3) pharmaceutical compositions of all the above peptides/peptide derivatives.

It is Applicant's understanding that this rejection is based primarily upon the perceived failure of the specification to provide working examples. Applicant notes that Section 2164.02 of the MPEP states that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed" and that the "specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation."

Applicant fails to see why the specification is unable to instruct one of ordinary skill in the art how to construct the claimed invention without undue experimentation. Applicant respectfully submits that the claim language that serves as the basis of the rejection is as follows: (1) a peptide consisting of between 6 and 25 amino acids comprising at least 6 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, and 19-39, including those wherein the peptide includes anchor positions for binding to alleles of MHC class II molecules DR3 and DR4, (2) a peptide or derivative thereof with a length between 6 and 25 amino acids which exhibits a specificity or/and affinity which is essentially equivalent to that of the peptide in (1) above, and/or includes anchor positions for binding to alleles of MHC class II molecules DR3 or DR4 and/or as pertains to SEQ ID NO: 19-39, has a length of at least 8 or 10

amino acids, and (3) pharmaceutical compositions of all the above peptides/peptide derivatives.

Applicant submits that this language sets forth an easy to comprehend list of requirements for the claimed peptides. Accordingly, Applicant is unable to see how one with ordinary skill in the art could find that this language would require undue experimentation given that it clearly states the requirements of the claimed peptides. Further, numerous examples of the claimed peptides can be found throughout the specification, but specifically on pages 4 and 5. Therefore, Applicant submits that the rejection is not well taken and requests that it be withdrawn.

Applicant also respectfully disagrees with the Office Action's statement that the claims are primarily defined by function. The claims set forth easy to understand requirements for what is intended to be claimed. Claim 46 and Claim 48 define the claimed peptides by the presence of requisite sequences, and not, as the Office Action states, primarily by function. While Applicant concedes that there is an affinity requirement, this, too, is governed by the presence of sequences equivalent to those already listed in the claim, and not by a final function of the claimed peptides. Thus, Applicant respectfully requests that the rejection be withdrawn.

The Office Action rejected Claims 46-54 under 35 U.S.C. 112, first paragraph, under the reasoning that they do not reasonably provide enablement for making and/or using an isolated peptide/derivative and pharmaceutical composition. The Office Action alleged that the specification has not enabled the breadth of the claimed invention in view of the teachings of the specification because the claims encompass peptides of

between 6 and 25 amino acid residues in length which contain at least 6 amino acid residues, potentially in non-contiguous order, from one of SEQ ID NO: 2, 3, or 19-39 and peptides of between 6 and 25 amino acid residues in length which are comprised of undisclosed amino acid residues other than anchor residues for binding to HLA-DR3 or HLA-DR4 and which exhibit a specificity or/and affinity which is essentially equivalent to that of the aforementioned peptides which contain at least 6 amino acid residues from SEQ ID NO: 2, 3, or 19-39.

The Office Action also stated that the state of the pertinent art is such that it is unpredictable in the absence of appropriate evidence whether the claimed invention can be made and/or used. The Office Action contended that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. This allegation was supported by noting that the specification discloses SEQ ID NO: 2, 3, and 19-39, but that it fails to disclose peptides or peptide derivatives of at least 6 amino acids and up to 25 amino acids from the group of SEQ ID NO: 2, 3, and 19-39, other than the previously discussed SEQ ID NO 4-18. Further, the Office Action took issue with the lack of a definition for "a specificity or/and affinity" which is "essentially equivalent to that of the aforementioned peptides." The Office Action also noted that the specification discloses that the term "essentially equivalent specificity or/and affinity of binding to MHC molecules" includes an improved binding specificity and/or affinity compared to amino acid sequences SEQ ID NO: 2, 3, or 19-39.

Additionally, it was noted that the specification discloses that an object of the invention is to provide new auto-reactive peptides which react with T cells from Type I

diabetics, and that this object is achieved by peptides or derivatives which bind analogously which are suitable for the detection, isolation, proliferation, anergization and/or elimination of auto-reactive T cells. The Office Action also observed that the specification discussed that the "anchor position" means an amino acid residue essential for binding to an MHC molecule and in particular to an MHC molecule of classes DR3, DR4 or DQ and that the anchor positions for the DRB10401 binding motif are given in the Hammer reference.

The Office Action stated that the Rammensee reference teaches that peptides of between about 6 and 25 amino acid residues in length bind to HLA-DR3 or HLA-DR4. The length of the peptide was noted as important for binding to HLA, along with the presence of anchor or motif amino acid residues present within the peptide. The Office Action advanced that an undue amount of experimentation would be involved in determining shorter peptides from the many possibilities that would be capable of binding to HLA-DR3 or DR4, and that it is unpredictable if those consisting of only 6 amino acid residues would be capable of binding at all. Additionally, the Office Action pointed out that the minimum amount of peptide required to span the binding groove and make favorable contacts may be dependent upon the sequence of the peptide itself since different amino acid residues have different physiochemical properties, and may be dependent upon the identity of the additional amino acids, since these residues may make a negative contribution to binding.

The Office Action cited the Ngo reference which teaches that the relationship between the sequence of a peptide and its tertiary structure is not well understood and is not predictable. Therefore, the Office Action advanced that there is a high level of

unpredictability in designing/selecting sequences that would still maintain function, and that applicant did not provide direction or guidance to do so. The Office Action found that because of this lack of guidance, extended experimentation would be required to determine which substitutions/deletions/additions or permutations of amino acids would be necessary to retain activity, and that it would require undue experimentation for one of skill in the art to arrive at other amino acid sequences that would have activity. The Office Action summarized the rejection by stating that because it would require undue experimentation to identify amino acid sequences that have functional activity, it would require undue experimentation to make and use the corresponding peptides. Thus, the Office Action concluded that undue experimentation would be required to determine what peptides could or could not be used in the claimed invention.

Applicant submits that this is an undue experimentation rejection. Applicant first notes that section 2164.01 of the MPEP states that "[a] patent need not teach, and preferably omits, what is well known in the art." Furthermore, it states that "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." Section 2164.01(a) states that "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole." Therefore, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention

without undue experimentation." Therefore a determination that undue experimentation is required is "reached by weighing all of the ... factual considerations [listed in *In re Wands*]." Lastly, Section 2164.04 places the burden of proving nonenablement upon the Examiner.

The Office Action has presented no reasons or evidence supporting the decision that the specification is nonenabling other than personal opinion. The Office Action has failed to consider many of the *Wands* factors, choosing to concentrate primarily upon the guidance provided in the specification. Additionally, the Office Action seems to require the applicant to discuss the means of experimentation to determine the applicability of the created peptides. Applicant submits that this technology and process is already well understood by those with ordinary skill in the art. Therefore, Applicant fails to see why the it would be required to explain such in the application. This is contrary to the requirements of the MPEP. Also contrary to the requirements of the MPEP is the Office Action's preoccupation with the time required to carry out any experimentation.

As stated above, the complexity of required experimentation does not make the experimentation undue. Because the Office Action has not provided any scientific evidence that the experimentation is more than complex, Applicant respectfully submits that this basis of rejection is also improper and requests that it be withdrawn.

The Office Action noted that the incorporation of essential material into the specification by reference to a foreign application, patent, or publication is improper. Thus, Applicant has amended the specification to include the material previously incorporated by reference to the Hammer reference. Applicant has attached a declaration stating that the amendatory material consists of the same material incorporated by reference in the referencing application, and that no new matter has been added. Thus, Applicant respectfully requests that this rejection be withdrawn.

Claims 46-54 were rejected under 35 U.S.C. 112, second paragraph, as indefinite. The Office Action stated that Claims 46 and 48 are indefinite in their recitation of "essentially equivalent" because it is not clear what essentially equivalent specificity and/or affinity of binding to MHC molecules entails. The Office Action advanced that the metes and bounds of the claims are not clear. As Applicant has amended the claims to remove the term "essentially," Applicant submits that the rejection has been overcome, and requests that it be withdrawn.

The Office Action also addressed priority and stated that, in regard to the application of prior art, the instant claims, as they pertain to SEQ ID NO: 19-39, are entitled to only the priority of the instant application because the scope of the claimed invention was not disclosed in parent applications 08/967,242 and 08/374,468, and because the foreign priority documents have not been provided and translated. The limitations the Office Action has stated are not supported by the parent applications are: (1) a peptide/peptide derivative composition thereof, comprising accessory stimulating

components and B7, derived from gad having a length of at most 25 amino acids and comprising a peptide of at least 6 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO: 19-39.

Applicant respectfully submits that this determination is not well taken. As stated earlier, these aspects of the claimed invention can be found in the original specification and claims. Accordingly, Applicant respectfully requests that the priority of the original filing date be granted to the sequences.

The Office Action rejected Claims 46-48 and 49-53 under 35 U.S.C. 102(b) as anticipated by WO 95/07992 (hereinafter the "'992 application"). The Office Action alleged that the '992 application teaches a 20-mer polypeptide that contains the sequence ILIKCDERGK which comprises at least 6 amino acid residues of a sequence from SEQ ID NO: 19. The '992 application also teaches that a peptide is linked to a label and the pharmaceutical administration of the claimed peptide. Additionally, the '992 application teaches that peptides from gad having at least one determinant for binding to T-cell receptor can be produced or chemically synthesized. Claims 46 and 48 were included in this rejection because they claim a "peptide derivative" which can be broadly read to read upon this art.

Additionally, the property of the peptide having anchor positions for binding to alleles of MHC class II molecules DR3 or DR4 is considered by the Office Action to be an inherent quality because the claimed peptide appears to be the same as the art

absent a showing of any differences. The Office Action has stated that the burden of proof is upon the applicant to demonstrate the difference between these peptides.

Applicant respectfully requests that this rejection be withdrawn in light of the previous amendments made to the claims. Applicant has amended the claim to cancel SEQ ID NO: 19. Thus, Applicant submits that the rejection has been overcome because the claims no longer read upon the disclosure of the '992 application.

Claims 52-54 were rejected by the Office Action under 35 U.S.C. 103(a) as obvious in light of WO 95/07992 in view of U.S. Patent No. 5,750,114 (hereinafter the "'114 patent") and U.S. Patent No. 6,060,309 (hereinafter the "'309 patent"). The Office Action explained that the WO 95/07992 reference teaches the same material as stated in the previous rejection while the '114 patent discloses pharmaceutical compositions comprising peptides and also immunomodulators such as IL-2 for human administration. The '114 patent also teaches that the choice of an adjuvant for the species of the individual being vaccinated when that species is human, depends partially upon whether or not the adjuvant has been approved for human use by the FDA. The Office Action cited to the '309 patent for its teaching of administration of gad peptides along with an adjuvant complete Freunds adjuvant (CFA) to mice.

Based upon these teachings, the Office Action stated that it would have been prima facie obvious to one of ordinary skill in the art at the time of invention to have added the adjuvant as disclosed in the '309 patent in the manner taught by the '114 patent (such as IL-2) to the gad peptide-containing pharmaceutical composition taught

by WO 95/07992. The Office Action explained that the motivation to combine would have been provided by the desire to immunomodulate an immune response to gad peptides as disclosed by the '114 patent in humans because the '309 patent discloses the administration of gad peptides along with an adjuvant CFA in mice. The Office Action also noted that one of ordinary skill would have recognized that the CFA adjuvant disclosed by the '309 patent was contraindicated for human usage due to the heat killed mycobacterial component in CFA.

Applicant submits that the claims, as amended, overcome this rejection, and requests that it be withdrawn

Applicant respectfully urges that, in light of the above amendments and discussion, the claimed invention is in condition for allowance and request early notification to that effect.

In the event this paper is not timely filed, Applicant hereby petitions for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other fees which may be due with respect to this paper.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300, referring to client-matter number 100564-09014.

Respectfully submitted,

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DDD/ddd
Enclosures: Marked-Up Copy of Specification
Marked-Up Copy of Claims
Change of Address
Claim for Priority
Certified Copies of P4403522.5, P4401629.8, and P4418091.8
Petition for Extension of Time (Two Months)
Sequence Declaration, hardcopy and disk

MARKED-UP COPY OF SPECIFICATION

Please insert on page 1, line 1: This application is a continuation of U.S. Application Ser. No. 08/967,242 filed on November 5, 1997 which is a continuation of U.S. Application Ser. No. 08/374,468 filed on January 18, 1995.

Page 25, lines 31-32: Fig. 1 shows autoreactive amino acid sequences (SEQ ID NOS: 19-22) according to the invention

Page 25, line 34,-Page 26, line 1: Fig. 2 shows further autoreactive amino acid sequences (SEQ ID NOS: 23-39)according to the invention

MARKED UP COPY OF CLAIMS

(once amended) 46. A peptide derived from glutamic acid decarboxylase having a length of at most 25 amino acids and comprising

(a) a peptide of at least 6 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NOS: 2, 3 and [19-39] 20-39, or

(b) a peptide or peptide derivative having a length of 6 to 25 amino acids which exhibits a specificity or/and affinity which is [essentially] equivalent to that of the peptide (a) and includes anchor positions for binding to alleles of MHC class II molecules DR3 or DR4, wherein the peptide derivative is not SEQ ID NO: 19.

(once amended) 48. The peptide of claim 46, wherein the peptide comprises

(a) a peptide of at least 6 amino acids of an amino acid sequence selected from the group consisting of SEQ ID NO: 2 and SEQ ID NO: 3, or

(b) a peptide or peptide derivative having a length of 6 to 25 amino acids which exhibits a specificity or/and affinity which is [essentially] equivalent to that of the peptide (a) and includes anchor positions for binding to alleles of MHC class II molecules DR3 or DR4, wherein the peptide derivative is not SEQ ID NO: 19.